Remarks

In view of the following remarks, reconsideration and withdrawal of the Examiner's rejections are requested respectfully.

Status of the Claims

The Examiner's Action addresses all pending claims, namely Claims 1 to 5 and 20 to 34. In addition, the Examiner's Action addresses Claims 10 to 19 which were cancelled, however, in applicants' Second Preliminary Amendment of January 22, 2001 which cancelled also Claims 6 to 9.

As to the pending claims, Claims 4, 23, 24, 28 to 30, and 33 to 34 have been amended. Claim 35 has been added. No claim has been cancelled.

Accordingly, Claims 1 to 5 and 20 to 35 are now presented for the Examiner's consideration.

Support for the Amendments to the Claims

Support for the amendments to Claim 4 is found in the specification on page 4, lines 15 to 20; page 8, lines 1 to 4; and on page 10, lines 11 and 12. Support for the amendments to Claims 23, 24, 28 to 30, 33, and 34 is found in specification on page 27, Table 7; page 31, Table 10; page 37, Table 18; page 39, Table 19; and page 41, Table 22. Support for new Claim 35 is found in the specification on page 4, lines 15 to 20, and in Claim 1 as originally filed. No new matter has been added.

Summary of the Examiner's Rejections

Claims 4, 5, 20 to 24, and 28 to 34 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. The rejection of cancelled Claims 10 to 19 is moot.

Claims 1 to 5, 20 to 22, 25 to 27, and 31 to 34 were rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 6,080,736 to Landry et al. (the Landry reference) in combination with U.S. Patent No. 6,066,339 to Stark et al. (the Stark reference). The rejection of cancelled Claims 11 to 14 and 19 is moot.

Claims 1 to 5, 10, 11 to 17, 20 to 24, 28 to 30, 35 to 37, 31, and 32 were rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 4,851,228 to Zentner et al. (the Zentner reference) in view of the Stark reference. The rejection of cancelled claims 11 to 14 is moot.

Summary of Applicants' Invention

Applicants' invention relates to a pharmaceutical formulation and method for treatment of depression or obsessive compulsive disorder by administering the formulation to a patient. According to an aspect of the invention, the formulation comprises: 1) particles of a selective serotonin reuptake inhibitor (SSRI) or a pharmaceutically acceptable salt thereof; and 2) a rate-controlling polymer coating which allows controlled release of an SSRI over a period of not less than about 12 hours.

SSRIs include fluoxetine, fluvoxamine, paroxetine, and sertraline, which may be available in tablet, suppository and injection forms. Fluvoxamine, for example, is conventionally administered in tablet form (25 mg, 50 mg, and 100 mg) as fluvoxamine maleate. Tablets including fluvoxamine are currently titrated gradually to a tolerated dose with maximum therapeutic benefit. Doses of greater than 100 mg are typically given in two divided doses, not to exceed 300 mg per day. Gradual titration and adverse events relating to conventional once-daily dosing of doses greater than 100 mg may, however, reduce patient compliance and delay the onset of therapeutic benefit.

The present invention provides advantageously a controlled release SSRI over a period of not less than about 12 hours following oral administration. The controlled release SSRI of the invention is suitable for oral administration once or twice daily; this is no more frequent, on the average, than at twelve hour intervals.

The SSRI particles of the formulation may take the form of pellets or beads which comprise a core. The core may also comprise an organic acid. The core is coated with a rate-controlling polymer which forms a rate-controlling membrane surrounding the core. The rate-controlling membrane is effective in providing a controlled release of an SSRI over a period of not less than about 12 hours following oral administration.

In one embodiment of the invention, the rate-controlling membrane comprises a pharmaceutically acceptable film-forming, water-insoluble polymer. In another embodiment of the invention, the rate-controlling membrane may also comprise a mixture of the aforementioned water-insoluble polymer and a pharmaceutically acceptable film-forming, water-soluble polymer component.

The discussion which follows demonstrates that the combined disclosures of the cited references do not render the present invention obvious. A summary of each reference and of the Examiner's rejections appears immediately below.

Summary of the References

The references cited by the Examiner in support of the § 103 rejection are summarized below.

U.S. Patent No. 6,080,736 to Landry et al.

The Landry reference relates to a method for utilizing the R enantiomer of tofisopam substantially free of the S enantiomer in the treatment of anxiety or anxiety disorders. The compound R-tofisopam is described as being administered before, along with, or after other psychoactive compounds, including fluvoxamine. See, column 16, lines 30 to 38 of the Landry reference.

The Landry reference is silent with regard to a rate-controlling coating, as acknowledged by the Examiner on page 4 of the Office Action. The Landry reference purports to disclose that the R-tofisopam compositions may be formulated to provide controlled release, but there are no examples disclosing a "rate-controlling polymer" coating "which allows controlled release . . . over a period of not less than about 12 hours", as recited in Claim 1 and the claims that depend therefrom. Fluvoxamine is disclosed in the Landry reference as being used only in conjunction with R-tofisopam, and no description with regard to the form of the fluvoxamine is provided. See, column 16, lines 30 to 44 of the Landry reference.

U.S. Patent No. 6,066,339 to Stark et al.

The Stark reference relates to an oral morphine multiparticulate formulation for once-daily administration comprising sustained release particles each having a core containing water-soluble morphine and an osmotic agent. The core is coated with a rate-controlling polymer comprised of ammonio methacrylate copolymers in an amount sufficient to achieve therapeutically effective plasma levels of morphine over at least 24 hours in the patient.

The Stark reference does not disclose the claimed release profile, as acknowledged by the Examiner on page 6 of the Office Action. The Stark reference also does not disclose the use of fluvoxamine or other SSRIs in combination with a rate-controlling polymer as recited in Claim 1 and the claims that depend therefrom.

U.S. Patent No. 4,581,228 to Zentner et al.

The Zentner reference relates to a multiparticulate osmotic pump for the controlled release of a pharmaceutically active agent to an environment of use. The pump comprises a carrier medium and multiple osmotic pump elements. The osmotic pump elements comprise a core composition mass or core mass of at least one pharmacologically active soluble agent, a rate controlling water-insoluble wall, a polymer permeable to water but impermeable to solute, and at least one pH insensitive pore-forming additive dispersed throughout the wall. The Zentner reference also describes the core composition mass as being in the form of a solid conventional tablet, pellet, or multiparticulate. The core mass is encased by a controlled porosity wall. See, column 10, lines 59 to 62. As disclosed in

the Zentner reference, the wall is composed of a polymeric material that is insoluble in fluids of the environment of intended use, and has a sponge-like structure composed of numerous open and closed cells through which the active agent is released after removal of the pore former.

The Zentner reference is silent with regard to the specific rate-controlled coating recited in Claims 5 and 32, as admitted by the Examiner. Although the Zentner reference, at columns 12 to 14, lists fluvoxamine in a lengthy list of drugs for possible use in the osmotic pump, there are no examples disclosing "particles of an SSRI . . .coated with rate-controlling polymer" for "controlled release" of an SSRI over a period of not less than about 12 hours following oral administration, as recited in Claim 1 and the claims that depend therefrom.

Discussion of the Examiner's Rejections

The § 112 rejection of the claims (second paragraph of § 112)

Claims 4, 23, 24, 28 to 30, 33, and 34 have been amended to define more clearly the invention. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

The § 103 Rejection based on the Landry and Stark References

The Examiner has asserted that a *prima facie* case of obviousness has been made. As set forth in the MPEP, Section 2143,

> "To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the publications themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or publications when combined) must teach or suggest all the claim limitations.
>
> The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)."

Contrary to the Examiner's assertion, a *prima facie* case of obviousness has not been made for the reasons which follow.

As discussed above, Claim 1, and the claims that depend therefrom, distinguish over the disclosures of the Landry and Stark references in reciting a multiparticulate controlled release SSRI formulation which comprises 1) particles of a SSRI or a pharmaceutically acceptable salt thereof, and 2) a rate-controlling polymer coating which allows controlled release of the SSRI over a period of not less than about 12 hours.

It is important to keep in mind that the Landry primary reference, when considered as a whole, is directed to administration of R-tofisopam, and only refers generally to controlled release of R-tofisopam. As a secondary matter, the Landry primary reference discloses that R-tofisopam may possibly be administered in conjunction with "other compounds", which compounds include fluvoxamine. The form of fluvoxamine, however, is not disclosed by the Landry primary reference, and neither is a rate-controlling coating, as acknowledged by the Examiner. There is simply no teaching or suggestion to a skilled

worker in the Landry primary reference that the "other compounds" used in conjunction with R-tofisopam, which compounds include fluvoxamine, may be 1) in the form of particles, or 2) include a rate-controlling polymer coating, as recited in Claim 1. Thus, the Landry primary reference does not teach or suggest a particulate form of an SSRI (such as fluvoxamine) or controlled release of an SSRI over not less than a 12 hour period as claimed.

The Stark secondary reference fails to cure the deficiencies of the Landry primary reference, since the Stark secondary reference fails to disclose the use of fluvoxamine or other SSRIs in any form whatsoever. The Stark secondary reference fails also to disclose the claimed release profile. By focusing on the result of "slow/controlled release formulation" of the Stark secondary reference to obtain the alleged expected result of "plasma levels of drug over at least 24 hours", the Examiner has clearly used applicants' disclosure in arriving at a conclusion of obviousness; this is improper since the teaching or suggestion to make the claimed combination must be found in the cited references.

Moreover, neither the Landry or Stark reference provides motivation to substitute an SSRI in particle form in the slow/controlled release formulation of the Stark reference for arriving at a result of "controlled release of said SSRI over a period of not less than about 12 hours" as recited in Claim 1. One skilled in the art would not have been motivated to substitute an SSRI in particle form, since the Landry primary reference does not disclose any particular form of fluvoxamine, and the Stark secondary reference does not disclose SSRIs or fluvoxamine. Furthermore, no motivation is provided by the either the Landry primary reference or the Stark secondary reference to omit the administration of R-tofisopam in favor of administration of fluvoxamine in particle form. The alleged

"similar" release profiles of the Stark secondary reference, without more, would not lead one skilled in the art at the time of the invention to modify the Landry primary reference as suggested by the Examiner and arrive at the invention as claimed. Therefore, since neither the Landry nor the Stark reference teaches, suggests, or provides motivation to use an SSRI, in particle form, for a controlled-release formulation which allows controlled release of the SSRI over a period of not less than about 12 hours, a *prima facie* case has not been made. Reconsideration and withdrawal of the rejection are requested respectfully.

The § 103 Rejection based on the Zentner and Stark References

The arguments set forth above concerning the inapplicability of the Stark reference and the arguments made with regard to the lack of *prima facie* obviousness are hereby reasserted as if set forth at length.

As discussed above, Claim 1 distinguishes over the disclosure of the Zentner and Stark references in reciting a multiparticulate controlled release SSRI formulation which comprises 1) particles of a SSRI or a pharmaceutically acceptable salt thereof, and 2) a rate-controlling polymer coating which allows controlled release of the SSRI over a period of not less than about 12 hours.

It is important to keep in mind that the Zentner primary reference, when considered as a whole, is directed to a multiparticulate osmotic pump that includes a rate-controlling water-insoluble wall and requires the use of a pore former. Fluvoxamine is generally disclosed in a lengthy list of drugs for possible use in the pump.

Although the Zentner primary reference purports to disclose fluvoxamine in particle form, none of the examples discloses the use of particulate fluvoxamine or any other SSRI in particulate form. Example 14 purports to disclose that potassium chloride may be administered as a single particle, but this still does not teach or suggest, to one skilled in the art after reading the Zentner primary reference, that particles of an SSRI may be administered as recited in Claim 1.

Moreover, none of the Examples discloses the use of particles of a SSRI coated with a rate-controlling polymer that provides a controlled release over not less than about 12 hours. Indeed, the examples of the Zentner primary reference only describe the release of potassium chloride (Examples 1 to 7, 12, 14, and 16), sodium indomethacin (Examples 8 and 9), and cyclobenzaprine HCl (Examples 10, 11, and 13). Furthermore, the Examiner has asserted, and applicants agree, that the Zentner primary reference is silent with regard to the teaching of the specific rate-controlled coating recited in Claims 5 and 32.

The addition of the Stark secondary reference fails to cure the deficiencies of the Zentner primary reference, since there is no teaching or suggestion to modify the Zentner primary reference by omitting the pore former in forming a controlled-porosity wall to arrive at the controlled-release formulation of the invention as claimed. Since the Zentner reference fails to exemplify the release of SSRI particles from a rate-controlling polymer coating, the addition of "similar" release profiles from the Stark reference, without more, is insufficient to render the claimed invention obvious.

Moreover, neither the Zentner nor the Stark references provide motivation to substitute the ammonio methacrylate copolymers of the Stark reference in the Zentner formulation to obtain a multiparticulate formulation based on the alleged "expected result" of "prolonged release" as alleged by the Examiner. The Examiner has again improperly focused on the alleged expected result, and apparently has used applicants' disclosure in arriving at a conclusion of obviousness. As stated above, the teaching or suggestion to make the claimed combination must be found in the cited references. If one were to substitute the ammonio methacrylate copolymers of the Stark reference in the Zentner formulation, as suggested by the Examiner, the result would still not reach the invention as claimed, since there is no teaching or suggestion to omit the pore former of the Zentner formulation to obtain a controlled release of an agent. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

Abstract

An Abstract is attached to this Amendment on a separate sheet.

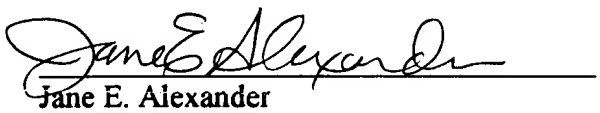
Claim for Priority

The specification has been amended to include reference to the applications from which priority is claimed.

Prior Art

The prior art made of record, but not relied upon, has been considered and a detailed discussion appears unnecessary.

Respectfully submitted,
Synnestvedt & Lechner LLP



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Version with Markings to Show Changes Made

Claim 4. (Once Amended) A formulation according to claim 3, wherein the rate-controlling membrane [is made up of] comprises a mixture of a major proportion of a pharmaceutically acceptable film-forming, water-insoluble polymer and [optionally] a minor proportion of a pharmaceutically acceptable film-forming, water soluble polymer in a selected ratio, the selected ratio of said water-insoluble polymer to said water-soluble polymer[, when said water-soluble polymer is present,] being effective to permit a SSRI release rate which allows controlled release of said SSRI over a period of not less than about 12 hours following oral administration.

Claim 23. (Once Amended) A formulation according to claim 1, wherein the SSRI release rate from the particles exhibits the following *in vitro* dissolution pattern when measured [*in vitro*] using a USP type II dissolution apparatus (paddle) according to US Pharmacopeia XXII in 0.05 M phosphate buffer at pH 6.8 [substantially corresponds to the following dissolution pattern]:

(a) no more than about 15% of the total SSRI is released after 0.5 of an hour of measurement in said apparatus;

(b) no more than about 25% of the total SSRI is released after 1 hour of measurement in said apparatus;

(c) between about 20% and about 75% of the total SSRI is released after 2 hours of measurement in said apparatus;

(d) not less than about 75% of the total SSRI is released after 4 hours of measurement in said apparatus; and

(e) not less than about 85% of the total SSRI is released after 6 hours of measurement in said apparatus.

Claim 24. (Once Amended) A formulation according to claim 1, wherein the SSRI release rate from the particles exhibits the following *in vitro* dissolution pattern when measured [*in vitro*] using a USP type II dissolution apparatus (paddle) according to US Pharmacopeia XXII in 0.05 M phosphate buffer at pH 6.8 [substantially corresponds to the following dissolution pattern]:

(a) no more than about 20% of the total SSRI is released after 4 hours of measurement in said apparatus;

(b) no more than about 45% of the total SSRI is released after 6 hours of measurement in said apparatus;

(c) between about 45% and 80% of the total SSRI is released after 8 hours of measurement in said apparatus;

(d) not less than about 70% of the total SSRI is released after 10 hours of measurement in said apparatus; and

(e) not less than about 80% of the total SSRI is released after 12 hours of measurement in said apparatus.

Claim 28. (Once Amended) A formulation according to claim 25, wherein the SSRI release rate from the particles exhibits the following *in vitro* dissolution pattern when measured [*in vitro*] using a USP type II dissolution apparatus (paddle) according to US Pharmacopeia XXII in 0.05 M phosphate buffer at pH 6.8 [substantially corresponds to the following dissolution pattern]:

(a) no more than about 20% of the total SSRI is released after 1 hour of measurement in said apparatus;

(b) no more than about 60% of the total SSRI is released after 2 hours of measurement in said apparatus;

(c) not less than about 20% of the total SSRI is released after 4 hours of measurement in said apparatus;

(d) not less than about 35% of the total SSRI is released after 6 hours of measurement in said apparatus;

(e) not less than about 50% of the total SSRI is released after 8 hours of measurement in said apparatus.

(f) not less than about 70% of the total SSRI is released after 10 hours of measurement in said apparatus; and

(g) not less than about 75% of the total SSRI is released after 12 hours of measurement in said apparatus.

Claim 29. (Once Amended) A formulation according to claim 25, wherein the SSRI release rate from the particles exhibits the following *in vitro* dissolution pattern when measured [*in vitro*] using a USP type II dissolution apparatus (paddle) according to US Pharmacopeia XXII in 0.05 M phosphate buffer at pH 6.8 [substantially corresponds to the following dissolution pattern]:

(a) no more than about 20% of the total SSRI is released after 1 hour of measurement in said apparatus;

(b) no more than about 45% of the total SSRI is released after 2 hours of measurement in said apparatus;

(c) between about 20% and about 70% of the total SSRI is released after 4 hours of measurement in said apparatus;

(d) between about 35% and about 85% of the total SSRI is released after 6 hours of measurement in said apparatus;

(e) not less than about 50% of the total SSRI is released after 8 hours of measurement in said apparatus.

(f) not less than about 70% of the total SSRI is released after 10 hours of measurement in said apparatus; and

(g) not less than about 75% of the total SSRI is released after 12 hours of measurement in said apparatus.

Claim 30. (Once Amended) A formulation according to claim 1, wherein the SSRI release rate from the particles exhibits the following *in vitro* dissolution pattern when measured [*in vitro*] using a USP type II dissolution apparatus (paddle) according to US Pharmacopeia XXII in 0.05 M phosphate buffer at pH 6.8 [substantially corresponds to the following dissolution pattern]:

(a) no more than about 50% of the total SSRI is released after 2 hours of measurement in said apparatus;

(b) not less than about 35% of the total SSRI is released after 6 hours of measurement in said apparatus; and

(c) not less than about 80% of the total SSRI is released after 22 hours of measurement in said apparatus.

Claim 33. (Once Amended) A method for the treatment of depression[,] or obsessive compulsive disorder [or other condition] treatable with an SSRI, comprising administering to a patient suffering from one of said conditions a therapeutically effective amount of a multiparticulate controlled release SSRI formulation according to claim 1.

Claim 34. (Once Amended) A method for the treatment of depression[,] or obsessive compulsive disorder [or other condition] treatable with an SSRI, comprising administering to a patient suffering from one of said conditions a therapeutically effective amount of a multiparticulate controlled release SSRI formulation according to claim 25.